REMARKS

The present invention relates to, among other things, novel methods for detecting a molecule (*e.g.*, an antigen) on a cell (*e.g.*, a blood cell), and novel reagents relating thereto.

The above-captioned application is a divisional application of U.S. Patent Application No. 08/884,046 (the "parent application"), now issued as U.S. Patent No. 5,985,543, to Siegel. The instant application was filed to prosecute original claims 10-23, which are drawn to an invention not elected in the parent application. By way of Preliminary Amendment filed in this application on September 29, 1999, claims 1-9 and 24-29, were canceled.

Subsequently, in Response to Restriction Requirement mailed September 25, 2001 (Paper No. 6), Applicant elected claims 10-19 for examination in this application. Accordingly, claims 10-23 are pending in this application, claims 20-23 stand withdrawn as being drawn to non-elected inventions, and claims 10-19 are under examination.

Finality of the Present Office Action

On March 10, 2005, Applicant's representative, Dr. Thomas Sossong, contacted Examiner Brown by telephone to discuss the finality of the present Office Action. Applicant thanks the Examiner for extending the courtesy of his consideration of this matter.

During the telephone call, Dr. Sossong explained that in the previous Office Action, issued on April 6, 2004 (Paper No. 11), the Examiner rejected only claim 11 as being indefinite under 35 U.S.C. § 112, second paragraph. In the previous response to the Office Action, filed on July 6, 2004, Applicant argued against the indefiniteness rejection of only claim 11, and Applicant did not make any amendments to any of the claims under consideration in the application. In the present Final Office Action, the Examiner has rejected claims 10-19 as being indefinite. Therefore, it appears that the Examiner's rejection of independent claim 10, and claims 12-19, which depend from claim 10, as being indefinite constitutes introduction of a new grounds of rejection not necessitated by Applicant's previous response.

Because the Examiner's rejection of claims 10 and 12-19 under 35 U.S.C. § 112, second paragraph, was not necessitated by Applicant's amendment of the claims, nor was it necessitated by a reference submitted to the Examiner in an Information Disclosure Statement as

described above, Dr. Sossong respectfully requested withdrawal of the finality of the present Office Action.

It is Applicant's understanding, based on the Interview Summary prepared and sent by the Examiner on March 10, 2005, that Examiner Brown acknowledged that, under the factual situation presented above, the finality of the Office Action mailed on November 16, 2004, was improperly set forth, and that the finality of the Office Action has been withdrawn and prosecution of the instant application will be reopened upon the Examiner's receipt of the present response to the November 16, 2004, Office Action. Applicant again thanks the Examiner for his open and willing cooperation in this regard.

Priority Claim

The Examiner has objected to the instant specification as not listing a claim of priority to U.S. Application No. 08/884,046, now U.S. Patent No. 5,985,543. Applicant respectfully disagrees, and directs the Examiner's attention to the Preliminary Amendment submitted at the time of filing of the present application, on September 29, 1999. This Preliminary Amendment specifically amended the as-filed application to include the priority claim indicating that the instant application is "a divisional of U.S. Application No. 08/884,046 filed on June 27, 1997."

Accordingly, Applicant respectfully submits that the instant application indeed properly claims priority to U.S. Application No. 08/884,046, now U.S. Patent No. 5,985,543, and that this priority claim was properly made at the time of filing.

Rejection of Claims 10-19 under 35 U.S.C. §112, first paragraph

Claims 10-19 stand rejected under 35 U.S.C. §112, first paragraph, because in the Examiner's opinion, the claims are not enabled. In the Examiner's view, the claims are not enabled in that the specification does not support a method for detecting cell agglutination in the absence of an incubation step. Applicant respectfully submits that method as recited by amended claims 10 and 11, as well as claims 12-19, which ultimately depend from claim 10, is enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

It is Applicant's understanding that the Examiner's rejection is based on the

requirement that the "second antibody must be given an opportunity to recognize, and interact with, the cell/bacteriophage complex" (see, e.g., the bottom of page 6 in the present Office Action). However, the majority of the Examiner's rejection as set forth in the Office Action is directed to the absence, from claims 10 and 11, of explicit claim language directed to "incubation" of the second antibody with the first antibody + cell complex, rather than to the binding of a second antibody with a first antibody-expressing phage, which binding precipitates agglutination. As Applicant argued in the previous response, and as set forth more fully below, the present invention does not "require" an incubation step, even though in various embodiments, the present invention may employ an incubation step, of varying lengths of time. Additionally, and as set forth more fully below, one skilled in the art, when armed with the present application, would be able to detect cell agglutination according to the amended claims – without an explicitly defined "incubation" step – without undue experimentation, which is the standard for enablement under the statute. Further, the instant specification, even if it provides an example teaching an incubation step, is merely illustrative and does not limit the invention in any way.

In any event, while not necessarily agreeing with the Examiner's reasoning, Applicant has herein amended claims 10 and 11 to reflect that the first antibody + cell complex must bind to the second antibody in order for agglutination to occur. Applicant respectfully submits that binding of the second antibody with the first antibody + cell complex, which complex includes a bacteriophage expressing the first antibody, is an element of the claimed invention of claims 10 and 11.

Support for these amendments can be found throughout the specification. For example, Applicant directs the Examiner's attention to the specification beginning at line 10 on page 22, extending through line 11 on page 23, which describes the desired interaction of a second antibody with a first antibody-expressing phage prior to agglutination, which described interaction can result in agglutination, but does not explicitly require any particular length of "incubation" for subsequent agglutination. Rather, because the processes of effecting and measuring agglutination are sufficiently well known in the art, Applicant respectfully submits that the skilled artisan, when armed with the present disclosure, will understand how to operate the present invention and to effect and measure agglutination in accordance with the present

invention. Further, Applicant respectfully submits that the claims do not need to recite an "incubation step," as the apparent purpose of the incubation step as described by the Examiner is to allow for binding of the second antibody to the first antibody-expressing phage + cell complex, the formation of which bound assembly subsequently can lead to agglutination.

The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

It is well-settled that an applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)).

Applicant respectfully submits that even though a working example is not required, the specification as filed sets forth several examples where the method of claims 10-19 was extensively reduced to practice. In these examples, Applicant demonstrated that cell agglutination could be readily detected using a mixture of cells and bacteriophage expressing an antibody specific for an antigen expressed by at least a portion of the cells in the mixture. Such examples are set forth at, *inter alia*, pages 43 through 44, and Figures 4, 5, and 6. Based on this ample reduction to practice, where the law does not require <u>any</u> reduction to practice, Applicant respectfully submits that the specification as filed provides enablement for a method of detecting cell agglutination as recited in claim 11, as well as that recited in claim 10, and claims depending therefrom.

Furthermore, as pointed out previously, the law is well-settled that extensive experimentation is not undue if one of ordinary skill in the art routinely engages in such experimentation. Moreover, the high degree of skill in the art, the extensiveness of

experimentation routinely performed by the artisan in that art, and the fact one skilled in the art of reference (*e.g.*, detection of cell agglutination) typically engaged in this type of experimentation at the time the application was filed, must all be considered. This is important, since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

Moreover, under the present law of enablement, generic claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), reviewing an enablement rejection of a broad claim reciting methods for producing insect proteins in cyanobacteria, the Court of Appeals for the Federal Circuit discussed enablement in the context of generic species claims:

> we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 20 USPQ2d at 1445 (emphasis added). Thus, not every species need be disclosed where one skilled in the art would be able, without undue experimentation, to determine which species possess the disclosed utility. *See also In re Druey*, 145 USPQ 219, 221 (Bd. Pat. App. & Int. 1965)("The fact that not all possible substituents encompassed by the generic language are illustrated does not preclude appellants from asserting the genus when no reasons have been advanced by the examiner to rebut appellants' assertion that all the compounds embraced by the genus will in fact have the properties ascribed to them."). Thus, each particular test condition need not be reduced to practice before the present claims are enabled.

The MPEP at § 2164.08(b), discussing inoperative subject matter, states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling.
> . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader that the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Thus, inoperative embodiments do not necessarily render a claim nonenabled as long as the experimentation required to identify the operative species is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen (HBsAg) using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known .
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the

art typically determines the assay conditions for detecting cell agglutination, one skilled in the art would not require undue experimentation to practice the invention commensurate with the scope of claims 10-19. Thus, where one skilled in the art routinely assesses and optimizes the conditions for allowing interaction of a second antibody with a first-antibody expressing bacteriophage, and for detecting cell agglutination resulting therefrom, as disclosed in the specification as filed, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted). Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for detecting cell agglutination are disclosed and exemplified in the specification, where methods for conducting and detecting second antibody-phage interactions are disclosed and exemplified in the specification, and where various conditions are extensively disclosed and reduced to practice in the specification as filed, it would not be undue experimentation to practice the method of the invention as disclosed in the present specification where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins (*i.e.*, mutated protein variants of the naturally-occurring protein) comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely determines the conditions for detecting cell agglutination, particularly after use of a second antibody, it is not undue experimentation for them to do so without the need to recite an incubation step. Similarly, where the invention discloses and, where examples demonstrate

extensive reduction to practice of the invention, every single assay condition for detecting cell agglutination following the teachings provided in the specification in light of the skill in the art need not be set out before such methods can be patented.

Indeed, one skilled in the art of performing assays for detecting cell agglutination would routinely assess and develop the conditions for performing the assay, including, but not limited to, how much, if any, incubation was required at each step of the assay, along with other parameters such as, *e.g.*, the conditions required for incubation of a second antibody with the reaction mixture, the concentrations of reagents, temperature of the reaction, and the like. These were all routine matters for experimentation by the skilled artisan at the time the specification was filed and, thus, no undue experimentation would be required by the skilled artisan in performing such manipulations.

Additionally, Applicant respectfully points out that the reference cited again by the Examiner for the proposition that it was known in the art that detecting agglutination required an incubation step, *i.e.*, U.S. Patent No. 5,491,067, to Setcavage et al., does not support that incubation is required in the novel agglutination detection methods of the invention. Applicant respectfully asserts that whatever Setcavage et al., may teach about detection of unknown antibodies in a serum or plasma sample using characterized cells, these teachings are inapplicable to the present invention which relates to detection of antigens present on an uncharacterized cell using well-characterized phage-displayed antibodies. Thus, the teachings of Setcavage et al., cannot be extended to the present invention where the reference teaches a completely different method relating to cell agglutination. That is, the present claimed invention teaches, *inter alia*, a method for detecting cell agglutination where the phage that is displaying the first antibody is bound by a second antibody specific for the phage. Subsequent to this binding, as described elsewhere herein, the detection of agglutination is well within the skill of the ordinary artisan who is armed with the specification of the instant application.

Further, it is well-settled that recitation of an example does not in any way limit the claims to that embodiment under present patent law. Thus, the recitation in the specification at page 24, line 23, pointed out by the Examiner to support that an incubation step is required in the method of the invention, merely illustrates that in one embodiment, incubation was performed. However, it is well-settled that providing an example does not limit the invention to

that example, and in no way limits the claim to that embodiment. Thus, mere recitation of an example reciting incubation does not support that claims that do not recite an incubation step are not enabled. Rather, the claims are interpreted in light of the specification as a whole and in view of the skill in the art, and are not limited to any particular exemplary embodiment provided to illustrate the invention. Otherwise, applicants for a patent would be compelled to provide numerous examples so as to avoid unwittingly narrowing their invention to any particular example set out in the specification. The present patent statute, and case law applying and expounding it, do not compel such a result.

Therefore, Applicant respectfully submits that the specification as filed amply supports that the claimed methods are enabled under 35 U.S.C. §112, first paragraph, and the rejection of claims 10-19, should be reconsidered and withdrawn.

Rejection of claims 10-19, pursuant to 35 U.S.C. §112, second paragraph

Claim 10-19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. As discussed in detail above, the Examiner has agreed that the present rejection of claims 10 and 12-19 pursuant to 35 U.S.C. § 112, second paragraph, constitutes a new grounds of rejection not necessitated by Applicant's amendment or argument. Because the Examiner has set forth that, upon receipt of the present response, prosecution will be reopened in the instant application, Applicant hereby addresses the Examiner's indefiniteness rejection of claims 10-19.

In the Examiner's opinion, claims 10-19 are indefinite in that the claims omit an essential step, *i.e.*, "incubating the mixture of cell/virus complexes with the inert particles prior to centrifugation." (Office Action at page 4). Applicant respectfully submits that claims 10-19 are not indefinite in any way for the following reasons.

It is settled law that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). *See also* MPEP § 2173.01. This is because "[t]he dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words, but words for things." *Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Further, applicant is entitled to have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Therefore, applicants are entitled to define terms to

describe their invention and the claims must be interpreted in light of the other parts of the application, including the disclosure in the specification and the definitions provided therein.

Applicant respectfully submits that claims 10 and 11, amended as set forth in detail above, now recite a step whereby a second, phage-specific antibody binds to a phage expressing on its surface a first antibody. As set forth above, it is Applicant's understanding that the Examiner's rejection is based on the requirement that the "second antibody must be given an opportunity to recognize, and interact with, the cell/bacteriophage complex" (see, e.g., the bottom of page 6 in the present Office Action). The claims now require the interaction between the second antibody and the phage-first antibody complex prior to agglutination, and therefore, the Examiner's rejection no longer applies.

Applicant also submits that the specification as filed makes clear that the method for detecting agglutination comprising sedimentation by centrifugation can, but need not, encompass an incubation step. That is, as previously discussed elsewhere herein, the skilled artisan, armed with the teachings provided in the specification as filed, would have understood that the reaction conditions could be readily determined for any phage-displayed antibody of interest to detect a known antigen expressed on a cell of interest present in a sample. Thus, there is absolutely nothing vague about claims 10-19 as presently set forth because the skilled artisan would have appreciated, at the time the application was filed, that the method can, but need not, comprise an incubation step, and the lack of recitation of such as step does not render the claim vague in any way. Thus, recitation of an incubation step is not essential, and claims 10-19, as amended, would be well understood by one skilled in the art and is not vague or indefinite in any way. Accordingly, Applicant respectfully requests that the rejection of claims 10-19 under 35 U.S.C. §112, second paragraph, for indefiniteness, be reconsidered and withdrawn.

Summary

Applicant respectfully submits that each of the Examiners rejections has been either overcome or is now inapplicable, and that each of claims 10-19 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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MARCH 22, 2005
(Date)

By: _____

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